

Increased nuchal traslucency in normal karyotype fetuses

Roberta De Domenico¹,
Marianna Faraci¹,
Entela Hyseni³,
Fosca A. F. Di Prima⁴,
Oriana Valenti²,
Santo Monte²,
Elsa Giorgio¹,
Eliana Renda⁵

¹ Policlinico Universitario "G. Martino",
Department of Obstetrics and Gynecology,
University of Messina, Italy

² S. Bambino Hospital, Department of Obstetrics and
Gynecology and Microbiological Sciences,
University of Catania, Italy

³ Campus Biomedico, Operative Unit of Gynecology,
University of Rome, Italy

⁴ Policlinico Hospital, Department of Obstetrics and
Gynecology, University of Catania, Italy

⁵ Policlinico Universitario "P. Giaccone",
Department of Obstetrics and Gynecology,
University of Palermo, Italy

Corresponding author:

Roberta De Domenico
Policlinico Universitario "G. Martino",
Department of Obstetrics and Gynecology,
University of Messina, Italy
via Consolare Valeria Messina
E-mail: dedom83@hotmail.com
Phone: +393496724072

Summary

Nuchal traslucency (NT) measurement between 11 and 14 weeks' gestation is a reliable marker for chromosomal abnormalities, including trisomy 21. However, even if conventional karyotyping is normal, increased NT is a predictive value of adverse pregnancy outcome, because it is associated with several fetal malformations, congenital heart defects, genetic syndromes, intrauterine death and miscarriages; the majority of these structural anomalies are undetectable before birth. The risk is proportional to the nuchal traslucency thickness, in fact it statistically increases after measurement reaching 3.5 mm or more. However, when these chromosomally normal fetuses with an enlarged NT survive, even if a detailed ultrasound examination and echocardiography fail to reveal any abnormalities, their uneventful outcome and postnatal developmental delay will be not statistically increased when compared to the ge-

neral population. These parents should be confidently reassured that the residual chance of structural anomalies and abnormal neurodevelopment may not be higher than in the general population.

Key Words: nuchal traslucency (NT); chromosomal abnormalities; first trimester screening.

Introduction

In the first trimester of pregnancy there is a subcutaneous collection of fluid in the fetal neck that is visualized by ultrasonography as a nuchal traslucency (NT)(1). The measurement should be made between 11 and 14 weeks but the best performance is obtained at 11-12 weeks (2). Normally NT thickness increases with fetal crown-rump length (CRL), in fact at a CRL of 45 mm is between 1.2 and 2.1 mm and at a CRL of 84 mm is 1.9 and 2.7 mm (median and 95th centile values) (3). The 99th centile is about 3.5 mm. The measurement has to be performed by qualified ultrasonographers undergoing regular quality assessment (4). In this article we review the association between increased fetal NT thickness in cromosomally normal fetuses and several fetal malformations, deformations, dysplasias and genetic syndromes (5); moreover we analyze which is the right approach with the parents of the euploid fetuses with enlarged NT (6).

Pathological correlation between increased NT and euploid fetuses

On the basis of three studies reporting on a total of 4991 euploid fetuses with increased NT it is possible to estimate that the prevalence of miscarriage or fetal death increases from 1.6% in those with NT between the 95th and 99th centiles to about 20% for NT of ≥ 6.5 mm (5, 7).

The prevalence of fetal death increases exponentially with NT thickness and these values are underestimated because the mortality rate should include cases of deteriorating fetal hydrops in which the 30% of couples decide to terminate pregnancy before intrauterine fetal death occurs (6).

Several studies have reported that increased fetal NT is associated with fetal abnormalities which means fetuses requiring medical and/or surgical treatment or conditions associated with mental handicap: from 1.6% in those with NT below 95th centile (8), to 2.5% for NT between the 95th and 99th centiles, until about 45% for NT of 6.5 mm or more (9,10).

Abnormalities associated with increased NT

Several abnormalities have been reported in fetuses with

enlarged NT, the major are cardiac defects, diaphragmatic hernia, exomphalos, body stalk anomaly, skeletal defects, and certain genetic syndromes, such as congenital adrenal hyperplasia, fetal akinesia, deformation sequence, Noonan syndrome, Smith-lemli-Opitz syndrome and spinal muscular atrophy and their incidence is higher than in the general population; instead anencephaly, holoprosencephaly, gastroschisis, renal abnormalities and spina bifida have the same prevalence that in the general population.

Cardiac defects

Regarding congenital cardiac defects, their prevalence is six times higher in fetuses with a NT $\geq 99^{\text{th}}$ percentile than in an unselected population (11-13). In chromosomally normal fetuses the most common abnormalities are narrowing of the aorta at the level of the isthmus and septal or valvular defects (14).

Eight studies have reported on the screening performance of NT thickness for the detection of cardiac defects (8, 15-18). In total, 67,256 pregnancies were examined, and the prevalence of major cardiac defects was 2.4 per 1,000. The detection rate of cardiac defects was 37.5% at a false positive rate of 4.9%. A meta-analysis of screening studies showed that specialist fetal echocardiography in all chromosomally normal fetuses with NT above the 99th centile would identify 1 major cardiac defect in every 16 patients examined; moreover the screening performance does not vary with the type of cardiac defect (19).

Increased nuchal translucency could constitute an indication for specialist fetal echocardiography, so it could be a substantially improved prenatal detection of congenital cardiac defects.

Study of ductus venosus (DV) flow patterns and tricuspid regurgitation (TR) may also improve the selection of those requiring specialized echocardiography (20, 21).

Sporadic abnormalities

Body stalk anomaly (BSA) is a sporadic polymalformative syndrome incompatible with extrauterine life. The fetus had a large anterior midline abdominal wall defect with eventration of the visceral organs into the amnio-peritoneal sac and a completely absent umbilical cord. We review that in an ultrasound screening study of 106,727 fetuses at 10 to 14 weeks, there were 14 cases of this anomaly and the fetal NT was increased in 84% of the fetuses, the karyotype was normal (22, 23).

Increased NT thickness is present in about 40% of fetuses with diaphragmatic hernia (24).

Increased NT is observed also in fetuses with exomphalos, in 85% chromosomally abnormal and in 40% chromosomally normal (5).

Megacystis is associated with increased NT, which is observed in about 75% of those with chromosomal abnormalities and in about 30% of those with normal karyotype (25).

Also rare genetic syndromes seem associated with increased NT but an indisputable association between their presence and nuchal translucency thickness is difficult to prove (5).

Mechanism of increased NT

There are a lot of condition associated with increased NT, probably because there are many possible mechanisms for this condition. One mechanism could be the cardiac dysfunction in association with abnormalities of the heart and great arteries, probably the heart failure contributes to increase NT, in the first trimester fetus only a small impairment of cardiac diastolic function is necessary to result in an increase NT and abnormal ductal flow (5).

Another mechanism could be venous congestion in the head and neck resulted from constriction of the fetal body as, for example, in the superior mediastinal compression in diaphragmatic hernia or the narrow chest in skeletal dysplasias (5).

In the nuchal skin of trisomy 21 fetuses there is an increase in hyaluronic acid that can entrap large amounts of solvent in the extracellular matrix (26). Many genetic syndromes are associated with alterations in collagen metabolism, this could be responsible of increased fetal NT (5).

Moreover NT could be increased by a failure of lymphatic drainage for its abnormal development or for impaired lymphatic drainage resulting from reduced fetal movements in neuromuscular disorders. Other mechanisms are fetal anemia, fetal hypoproteinemia and parvovirus B19 fetal infection (5).

Management of euploid fetuses with increased NT

We reviewed the correlation between NT thickness and abnormalities, chromosomal defects, miscarriage and fetal death. On the basis of this data it is possible to plan the appropriate follow-up investigations and to counsel parents of these fetuses with increased NT.

With NT value below the 99th centile (3.5 mm) the decision in favor or against fetal karyotyping will be based on the patient-specific risk for chromosomal defects which depends on the first trimester screening, calculated on the basis of maternal age, sonographic findings and serum free β -hCG and PAPP-A at 11 to 14 weeks (27, 28). The chances of having a baby with no major abnormalities is about 97% for NT below the 95th centile and 93% for NT between the 95th and 99th centiles. However these fetuses will be undergone detailed fetal scan at 20 weeks to diagnose or exclude major malformations and abnormalities.

With fetal NT above 3.5 mm a fetal karyotyping by CVS should be offered, in addition a detailed scan at 11 to 13+6 weeks should be carried out; in those cases in which fetal karyotype is normal but NT is above 3.5 mm should be offered fetal echocardiography at 14 to 16 weeks. After this it will be necessary to make the detailed scan carried out by the general population at 20 to 22 weeks for the exclusion or diagnosis of major abnormalities and malformations.

If these investigations demonstrate absence of major abnormalities the parents should be informed that they have the same probability of the general population to delivery a baby with serious abnormality or neurodevelopmental delay (5).

If increased NT persists at 14 to 16 weeks scan or it becomes nuchal edema at 20 to 22 weeks, it should be considered the possibility of congenital infection or a genetic syndrome, parents should be also informed that there is a 10% risk of evolution to hydrops and perinatal death

or the possibility of a genetic syndrome, such as Noonan syndrome (10). Moreover the risk of neurodevelopmental delay is 3% to 5%.

Conclusion

Increased NT is an expression, and so an useful marker, of chromosomal abnormalities, fetal malformations and genetic syndromes; the chance of an uneventful pregnancy outcome is inversely related to the initial degree of enlargement.

On the basis of the data reviewed the chances of delivering a baby with no major abnormalities are only about 70% for NT of 3.5-4.4 mm, 50% for NT of 4.5-5.4 mm, 30% for NT of 5.5-6.4 mm, and 15% for NT of 6.5 or more. The parents have to be informed on the need to undergo extra investigations and to take counsel with a geneticist. When investigations are normal and the increased NT resolves, parents should be confidently reassured that the possibility of adverse outcome may be not higher than in a general population. Finally the majority of fetal abnormalities associated with increased NT can be detected by investigations that can be satisfied at 14 weeks of gestation.

References

- Nicolaides KH, Azar G, Byrne D, Mansur C, Marks K. Fetal nuchal translucency: ultrasound screening for chromosomal defects in first trimester of pregnancy. *BMJ* 1992;304:867-89.
- Malone FD, Canick JA, Ball RH, et al. First-trimester or second-trimester screening, or both, for Down's syndrome. *N.Engl.J.Med.* 2005; 353(19): 2001-2011.
- Snijders RJM, Noble P, Sebire N, Souka A, Nicolaides KH. UK multicentre project on assessment of risk of trisomy 21 by maternal age and fetal nuchal translucency thickness at 10-14 weeks of gestation. *Lancet* 1998;351:343-6.
- Evans MI, Van DH, Nicolaides KH. 2007. Nuchal translucency measurements for first-trimester screening: the 'price' of inaccuracy. *Fetal Diagn. Ther.* 22(6): 401-404.
- Souka AP, von Kaisenberg CS, Hyett JA, Sonek JD, Nicolaides KH. Increased nuchal translucency with normal karyotype. *Am.J.Obstet.Gynecol.* 2005; 192(4): 1005-1021.
- Bilardo CM, Timmerman E, Pajkrt E, Van Maarle M. Increased nuchal translucency in euploid fetuses- what should we be telling the parents?. *Prenat Diagn.* 2010; 30:93-102.
- Bilardo CM, Müller MA, Pajkrt E, Clur SA, van Zalen MM, Bijlsma EK. Increased nuchal translucency thickness and normal karyotype: time for parental reassurance. *Ultrasound Obstet Gynecol* 2007; 30(1): 11-18.
- Michailidis GD, Economides DL. Nuchal translucency measurement and pregnancy outcome in karyotypically normal fetuses. *Ultrasound Obstet Gynecol* 2001;17:102-5.
- Souka AP, Snijders RJM, Novakov A, Soares W, Nicolaides KH. Defects and syndromes in chromosomally normal fetuses with increased nuchal translucency at 10-14 weeks of gestation. *Ultrasound Obstet Gynecol* 1998;11:391-400.
- Souka AP, Kramp E, Bakalis S, Heath V, Nicolaides KH. Outcome of pregnancy in chromosomally normal fetuses with increased nuchal translucency in the first trimester. *Ultrasound Obstet Gynecol* 2001;18:9-17.
- Ghi T, Huggon IC, Zosmer N, Nicolaides KH. Incidence of major structural cardiac defects associated with increased nuchal translucency but normal karyotype. *Ultrasound Obstet.Gynecol.* 2001; 18(6): 610-614.
- Atzei A, Gajewska K, Huggon IC, Allan L, Nicolaides KH. Relationship between nuchal translucency thickness and prevalence of major cardiac defects in fetuses with normal karyotype. *Ultrasound Obstet Gynecol* 2005; 26(2): 154-157.
- Clur SA, Mathijssen IB, Pajkrt E, et al. Structural heart defects associated with an increased nuchal translucency: 9 years experience in a referral centre. *Prenat Diagn* 2008; 28(4): 347-354.
- Hyett J, Moscoso G, Papapanagiotou G, Perdu M, Nicolaides KH. Abnormalities of the heart and great arteries in chromosomally normal fetuses with increased nuchal translucency thickness at 11-13 weeks of gestation. *Ultrasound Obstet Gynecol* 1996;7:245-50.
- Schwarzler P, Carvalho JS, Senat MV, Masroor T, Campbell S, Ville Y. Screening for fetal aneuploidies and fetal cardiac abnormalities by nuchal translucency thickness measurement at 10-14 weeks of gestation as part of routine antenatal care in an unselected population. *BJOG* 1999;106:1029-34.
- Bilardo CM, Pajkrt E, de Graaf IM, Mol BWJ, Bleker OP. Outcome of fetuses with enlarged nuchal translucency and normal karyotype. *Ultrasound Obstet Gynecol* 1998;11:401-6.
- Josefsson A, Molander E, Selbing A. Nuchal translucency as a screening test for chromosomal abnormalities in a routine first trimester ultrasound examination. *Acta Obstet Gynecol Scand* 1998;77:497-9.
- Hafner E, Schuller T, Metzenbauer M, Schuchter K, Philipp K. Increased nuchal translucency and congenital heart defects in a low-risk population. *Prenat Diagn* 2003;23:985-9.
- Makrydimas G, Sotiriadis A, Ioannidis JP. Screening performance of first-trimester nuchal translucency for major cardiac defects: a meta-analysis. *Am J Obstet Gynecol* 2003;189:1330-5.
- Maiz N, Valencia C, Emmanuel EE, Staboulidou I, Nicolaides KH. Screening for adverse pregnancy outcome by ductus venosus Doppler at 11-13 + 6 weeks of gestation. *Obstet.Gynecol.* 2008; 112(3): 598-605.
- Faiola S, Tsoi E, Huggon IC, Allan LD, Nicolaides KH. Likelihood ratio for trisomy 21 in fetuses with tricuspid regurgitation at the 11 to 13 + 6-week scan. *Ultrasound Obstet.Gynecol.* 2005; 26(1): 22-27.
- Daskalakis G, Sebire NJ, Jurkovic D, Snijders RJM, Nicolaides KH. Body stalk anomaly at 10-14 weeks of gestation. *Ultrasound Obstet Gynecol* 1997;10:416-8.
- Smrcek JM, Germer U, Krokowski M, Berg C, Krapp M, Geipel A, et al. Prenatal ultrasound diagnosis and management of body stalk anomaly: analysis of nine singleton and two multiple pregnancies. *Ultrasound Obstet Gynecol* 2003;21:322-8.
- Sebire NJ, Snijders RJM, Davenport M, Greenough A, Nicolaides KH. Fetal nuchal translucency thickness at 10-14 weeks of gestation and congenital diaphragm

- ragmatic hernia. *Obstet Gynecol* 1997;90:943-7.
25. Liao AW, Sebire NJ, Geerts L, Cicero S, Nicolaides KH. Megacystis at 10-14 weeks of gestation: chromosomal defects and outcome according to bladder length. *Ultrasound Obstet Gynecol* 2003;21:338-41.
26. Bohlandt S, von Kaisenberg CS, Wewetzer K, Christ B, Nicolaides KH, Brand-Saberi B. Hyaluronan in the nuchal skin of chromosomally abnormal fetuses. *Hum Reprod* 2000; 15:1155-8.
27. Spencer K, Souter V, Tul N, Snijders R, Nicolaides KH. A screening program for trisomy 21 at 10-14 weeks using fetal nuchal translucency, maternal serum free β -human chorionic gonadotropin and pregnancy-associated plasma protein-A. *Ultrasound Obstet Gynecol* 1999;13:231-7.
28. Wapner R, Thom E, Simpson JL, Pergament E, Silver R, Filkins K, et al. First trimester maternal serum biochemistry and fetal nuchal translucency screening (BUN) study group. First trimester screening for trisomies 21 and 18. *N Engl J Med* 2003; 349:1405-13.